REMARKS

This application has been amended in a manner that is believed to place it in condition for allowance at the time of the next Official Action.

Claims 33-35 and 38-46 are pending in the present application. Claim 33 has been amended to address the formal matters raised in the outstanding Official Action. Additionally, claim 33 has been amended to further characterize steps a), b), c) and d) in the present application. Support for amended claim 33 may be found in the original claims and generally throughout the specification. New claims 43-46 have been added. Support for new claims 43-44 may be found in claims 36-37. Claims 45-46 are supported at page 7, lines 1-15 in the present specification. Claims 36-37 have been cancelled.

In the outstanding Official Action, claims 33-42 were objected to for allegedly containing several informalities. Applicants believe that claims 33-42 and new claims 43-46 have been amended and/or drafted in a manner so as to obviate the objections.

Claims 33, 36, 37 and 40-41 were rejected under 35 USC 102(b) as allegedly being unpatentable over NILSSON et al. Applicants believe the present amendment obviates this rejection.

Applicant respectfully submits that NILSSON fails to anticipate or render obvious the claimed method of detecting a target nucleic acid sequence. In particular, NILSSON does not

teach a step of providing an oligonucleotide probe immobilized to a solid support (see claim 33, step a). Furthermore, there is no recognition of an immobilized probe comprising two end parts having at least one 3'-end sequence and at least one 5'-end sequence, wherein one of the end parts is provided with a solid phase anchor by which the probe is immobilized to the support and wherein said other end part comprises:

i) at least one detectable function and a cleavable site which lies between the detectable function and the solid phase anchor, or

ii) at least one detectable function provided on a dissociable part of the probe.

Indeed, the padlock probes taught by NILSSON are not immobilized. Rather, the target nucleic acid sequences are immobilized. As a result, it is not consistent with the claimed recitations to interpret the immobilized target nucleic acid sequence (or the part of it which hybridizes to the probe) as being the solid phase anchor. The solid phase anchor is part of the probe itself, before it is contacted with the target sequence. Thus, the probe is immobilized without the use of the target sequence.

Furthermore, NILSSON does not teach a step of cleaving as recited in claim 33, step d). Step (d) recites alternative steps of "cleaving the probe at the cleavage site" or "dissociating said dissociable probe part". Additionally, step

d) provides that if it the probe is circularized, the part of the probe comprising the detectable function becomes covalently connected to the probe part which has the solid phase anchor and therefore to the support, and hence cannot be detached (or de-connected) from the immobilized probe by the cleavage or dissociation step. If, on the other hand, the probe is not circularized, the probe part containing the detectable function is not covalently connected to the probe part containing the solid phase anchor and hence is not covalently connected to the support and can be detached (or de-connected) from the immobilized probe by the cleavage or dissociation step.

Thus, step (d) of claim 33 makes it clear that if the probe is not circularized, the part of the probe which carries the detectable function may be dissociated (de-connected) from the remaining part of the probe which is immobilized. NILSSON does not disclose such an embodiment where a part of the probe is dissociated. Thus, it is believed that this is distinct from the entire padlock probe of NILSSON, which is itself detectable and is dissociable from the immobilized target nucleic acid sequence by the denaturing wash.

As to new claims 43-44, applicants respectfully submit that NILSSON fails to disclose or suggest the utilization of a second padlock probe. NILSSON does not disclose any embodiments in which two padlock probes are used, one of which is dissociable from the other if there is no ligation. While the Office Action

refers to a "further circularizable probe" in NILSSON, applicants respectfully a further probe as claims is not disclosed. The legend to Figure 4 refers only to a circularizable target-specific probe which is biotinylated. A second padlock probe as recited in the claims is not taught.

Claims 45 and 46 recite that the cleavage site recited in the claimed method is a disulphide or a deoxyuridine residue or a peptide residue or a nucleotide sequence susceptible to cleavage by endonuclease, wherein cleavage of the oligonucleotide probe takes place using a cleaving agent being a reducing agent, a uracil DNA glycosylase, a peptidase or an endonuclease, respectively. Upon reviewing NILSSON, it is respectfully submitted that NILSSON fails to disclose or suggest such a recitation.

Claims 34, 35 and 42 were rejected under 35 USC 103(a) as allegedly being unpatentable over NILSSON et al. and further in view of URDEA et al. Applicants believe the present amendment obviates this rejection.

The claimed invention is based upon the presence within the probe of a solid phase anchor by which the probe is immobilised prior to its contact with the target sequence. As recited in amended claim 33 and as explained above, this enables the signal from the "detectable function" to be "anchored" to the solid support via the probe, when the probe is circularized following binding to its target sequence.

NILSSON neither discloses nor suggests such an embodiment. Rather, NILSSON is concerned with immobilised target sequences and not with probes which are immobilised independently of the target.

In an effort to remedy the deficiencies of NILSSON et al. for reference purposes, the Office Action cites to URDEA et al. However, URDEA et al are not concerned with padlock probes such as claimed. Thus, it is believed that URDEA et al. fails to remedy the deficiencies of NILSSON.

Furthermore, claims 34 and 35 encompass the embodiments wherein (at least) one of the probe ends has at least two branches. It is believed that this stands in contrast to the teachings of URDEA et al. URDEA et al disclose the use of nucleic acid multimers which comprise a first part capable of hybridising to the target sequence and a second part consisting of a branched structure composed of multiple copies of a single nucleic acid sequence that is complementary to a labelled nucleic acid.

The purpose of these multimers is to amplify the signal from nucleic acid hybridisation assays: for every one multimer which binds a single copy of a target sequence, multiple copies of identical, labelled probe sequences can bind the multiple copies of their complementary sequence of which the branched portion of the multimer is composed (see

column 2, lines 30-38, column 14 lines 57-68 and column 16 lines 32-39).

Thus, this is in contrast to the branched structures used in the present invention whereby non-identical probe ends are used for the detection of sequence variants present in a sample and not for the amplification of the signal generated via binding of the target sequence. Accordingly, applicants respectfully submit that the URDEA et al publication is not relevant to the instant application and would not have taught one skilled in the art the use of branched or bifurcated probe ends at the time the application was filed.

Claim 42 is directed to the embodiment wherein the oligonucleotide probe(s) are immobilised via biotin to a streptavidin-coated solid phase. While the Office Action correctly notes that column 16, lines 29-31 relate to a probe that can be attached to a solid phase via "biotin/avidin", this does not relate to a suitable cleavable linker molecule because the biotin/avidin linkage of the probe to the solid phase is not an example of the incorporation of suitable cleavable linker molecules at predetermined sites in the multimer.

Moreover, it is believed that the purpose of introducing such cleavable linkers into the multimer is for the stated purpose of "analysing the structure of the multimer or as a means for releasing predetermined segments (such as

the portion of the multimer that binds to the labelled oligonucleotide)". There is no teaching towards the use of linkers to effect the release of a detectable function in the absence of target binding.

Thus, applicants respectfully submit that the general teaching of multimers for use in amplifying the signal from the binding of a single target nucleic acid would not be deemed relevant to the subject matter of the present invention by the skilled artisan. As a result, one skilled in the art would lack the motivation to combine and modify the publications in a manner so as to obtain the claimed invention.

Claims 38 and 39 were rejected under 35 USC 103(a) as allegedly being unpatentable over NILSSON et al. and further in view of BIRKENMEYER et al. Applicants believe the present amendment obviates this rejection.

As noted above, the claimed invention relates to a probe of a solid phase anchor, wherein the probe is immobilised prior to its contact with the target sequence. Applicants also argue that NILSSON neither discloses nor suggests such an embodiment. Rather, NILSSON is concerned with immobilised target sequences and not with probes which are immobilised independently of the target.

In an effort to remedy the deficiencies of NILSSON et al. for reference purposes, the Office Action also cites to BIRKENMEYER et al. However, like URDEA et al, BIRKENMEYER et

al. are not concerned with the claimed padlock probes. Thus, it is believed that BIRKENMEYER et al. fail to remedy the deficiencies of NILSSON for reference purposes.

Indeed, BIRKENMEYER et al. relates to an improvement to the ligase chain reaction. BIRKENMEYER et al. teach the use of at least one recessed probe so that a gap is formed between adjacent probes when they are hybridised to a target. The gap is then filled in a target-dependent fashion prior to covalent ligation of the probe ends.

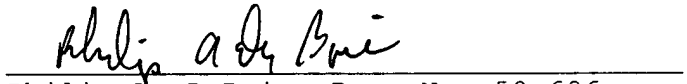
This stands in contrast to claim 38, wherein the target-specific probe is designed to hybridize to the target nucleic acid sequence to leave an interspace between the probe ends, at least one additional probe is provided which is designed to hybridize to the target nucleic acid sequence in the interspace, and the hybridized probes are then covalently interconnected.

In view of the present amendment and foregoing Remarks, therefore, applicant believes that the present application is in condition for allowance at the time of the next Official Action. Allowance and passage to issue on this basis is respectfully requested.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON



Philip A. DuBois, Reg. No. 50,696
745 South 23rd Street
Arlington, VA 22202
Telephone (703) 521-2297
Telefax (703) 685-0573
(703) 979-4709

PD/lk